Activity of meropenem, against gram-positive bacteria

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Abstract: A new carbapenem antibiotic, meropenem, was shown to be active against a large number of Gram-positive bacteria. The drug inhibited penicillinase-positive and -negative, methicillin-susceptible staphylococci equally well. Among the comparative antimicrobials examined, only N-fonnimidoyl-thienamycin (imipenem) was two to four times more active than meropenem. Compared with vancomycin or methicillin, meropenem was 10-20 times more active. Strains of 11 species of streptococci were highly susceptible to meropenem; the geometric mean MICs of the drug for these species ranged from 0.01 to 0.04mg/l. The agent, however, only had moderate activity against Enterococcus faecalis (mean MIC 5mg/l) and Ent. faecium (mean MIC 11.6 mg/l). Among Corynebacterium jeikeium, strains were encountered that showed susceptibility to meropenem but resistance to imipenem and other -lactams. Strains of other corynebacteria, Rhodococcus equi, Erysopelothrix rhusio-pathiae, Listeria monocytogenes, and Bacillus spp. all were highly susceptible to meropenem (mean MICs 0.04-0.17 mg/l). Although methicillin-resistant staphylo-cocci were inhibited by concentrations of 1-2 mg/l of meropenem in agar dilution tests, such strains showed heteroresistance in population studies, as is typical for all -lactam antibiotics. In addition, the biochemical correlate of methicillin-resistance, penicillin-binding protein 2 , showed low affinity for meropenem, similar to that for imipenem. Meropenem was as bactericidal as imipenem and comparative bactericidal antimicrobials in killing-curve experiments. Strains of Ent. faecium, C. jeikeium, and L. monocytogenes were killed at a slower rate than streptococci or staphylococci

DOI: https://doi.org/10.1093/jac/24.suppl_a.101

Journal of Antimicrobial Chemotherapy (1989) **24**, *Suppl. A*, 101–112

Activity of meropenem, against Gram-positive bacteria

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A new carbapenem antibiotic, meropenem, was shown to be active against a large number of Gram-positive bacteria. The drug inhibited penicillinase-positive and -negative, methicillin-susceptible staphylococci equally well. Among the comparative antimicrobials examined, only *N*-formimidoyl-thienamycin (imipenem) was two to four times more active than meropenem. Compared with vancomycin or methicillin, meropenem was 10–20 times more active. Strains of 11 species of streptococci were highly susceptible to meropenem; the geometric mean MICs of the drug for these species ranged from 0·01 to 0·04 mg/l. The agent, however, only had moderate activity against *Enterococcus faecalis* (mean MIC 5 mg/l) and *Ent. faecium* (mean MIC 11·6 mg/l). Among *Corynebacterium jeikeium*, strains were encountered that showed susceptibility to meropenem but resistance to imipenem and other β-lactams. Strains of other corynebacteria, *Rhodococcus equi, Erysopelothrix rhusiopathiae, Listeria monocytogenes*, and *Bacillus* spp. all were highly susceptible to meropenem (mean MICs 0·04–0·17 mg/l). Although methicillin-resistant staphylococci were inhibited by concentrations of 1–2 mg/l of meropenem in agar dilution tests, such strains showed heteroresistance in population studies, as is typical for all β-lactam antibiotics. In addition, the biochemical correlate of methicillin-resistance, penicillin-binding protein 2′, showed low affinity for meropenem, similar to that for imipenem. Meropenem was as bactericidal as imipenem and comparative bactericidal antimicrobials in killing-curve experiments. Strains of *Ent. faecium, C. jeikeium*, and *L. monocytogenes* were killed at a slower rate than streptococci or staphylococci.

Introduction

This study was undertaken to compare the in-vitro activity of meropenem with those of imipenem and various other antimicrobials against Gram-positive organisms. Special emphasis in our study was given to the bactericidal activity of meropenem, which was determined in killing-curve experiments.

Materials and methods

Bacteria

The bacteria used were isolated from clinical material and were identified according to standard procedures. Unusual organisms of no or only low pathogenic potential were included in order to obtain an overview of the Gram-positive spectrum of the drug. The strains *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used for quality control.

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Antibiotics

Stock solutions of meropenem and ciprofloxacin were prepared in sterile distilled water. Stock solutions of the other drugs were prepared as recommended by the NCCLS (1987). Stocks of meropenem and imipenem were freshly prepared for each experiment. The other stock solutions were stored at −80°C. All drugs were kindly provided as laboratory powders by the respective pharmaceutical companies.

Minimal inhibitory concentration tests

MICs were determined by an agar dilution procedure (NCCLS, 1985, 1987) with Mueller–Hinton (MH) agar (BBL) for staphylococci and Mueller–Hinton agar supplemented with 7% human blood for all other organisms. Staphylococci were tested on Mueller–Hinton agar as well as on Mueller–Hinton agar supplemented with 4% NaCl (Jorgensen, 1986) in order to detect methicillin-resistance. MICs of methicillin were read after incubation at 35°C for exactly 24 h. Methicillin-resistance was suggested when growth was observed on the plate containing 8 mg/l. MICs of the other β-lactam antibiotics were then compared in order to make a final decision about the presence of methicillin-resistance.

Bactericidal tests

Selected staphylococcal strains grown on blood agar were suspended in MH broth to approximately 10^6–10^7 cfu/ml. All other organisms were taken from blood agar and suspended in MH broth supplemented with cations and 2·5% lysed horse blood (NCCLS, 1987). Antibiotics were added in concentrations of ½, 1, 2, 4 and 8 times the MIC, respectively. One culture served as growth control. Incubation was carried out at 37°C in a water bath. At appropriate time intervals, samples were withdrawn and plated undiluted or in appropriate dilutions on to blood agar plates to determine the viable count. When necessary, β-lactam antibiotics in samples were inactivated by adding 12·5 U/ml of a mixture of four penicillinases (Porton Products Ltd, Salisbury, Wiltshire, UK), and incubating the samples at room temperature for at least 10 min before plating. Inactivation of β-lactams including the carbapenems was confirmed by a qualitative disc diffusion test.

Population studies

Populations of methicillin-resistant and -susceptible staphylococci were analysed by disaggregation of overnight broth cultures (briefly, by ultrasonication at 20 kHz) and surface inoculation of appropriate dilutions on L-agar (Berger–Bächi, Strässle & Kayser, 1986) containing increasing amounts of meropenem. Colony-forming units were counted after 48 h of incubation at 35°C.

Penicillin-binding proteins

Affinity of β-lactam antibiotics for penicillin-binding proteins (PBPs) prepared from cell membranes was examined in competition assays with radioactive benzylpenicillin, by a procedure slightly modified from that described recently by Berger–Bächi *et al.* (1986). Membrane preparations were incubated for 10 min at 37°C in the presence of 0,

0·5, 5, 50 and 500 mg/l of either meropenem or imipenem before reaction with 10 mg/l ^{3}[H]-labelled benzylpenicillin-ethyl-piperidinium salt (25 Ci/mmol, Merck, USA) for 10 min at 37°C. 50 μg protein was loaded per slot. PBPs were separated by SDS polyacrylamide gel electrophoresis. The acrylamide to NN′ methylene *bis*-acrylamide ratio was 3·75–0·1% in the stacking gel and 10–0·13% in the running gel. PBPs were detected by scintillation fluorography with NEN enhancer (New England Nuclear, USA) and exposing the gels at −70°C to Fuji RX1 film.

Results

Comparison of meropenem with other antimicrobials against Gram-positive bacteria

Table I summarizes the MICs of meropenem and other drugs for Gram-positive bacteria. Meropenem showed excellent activity against methicillin-susceptible staphylococci, whether they produced penicillinase or not. The drug was 12–14 times more active than methicillin. Imipenem was three to five times more active than meropenem against these strains. All of the eleven streptococcal species tested were highly susceptible to meropenem and to imipenem. Both drugs, however, exhibited only moderate activity against *Enterococcus faecalis*, and were of rather low activity against *Ent. faecium*.

Corynebacterium jeikeium has been associated with infections in immunosuppressed patients (Young *et al.*, 1981). The organism has also been isolated occasionally from cases of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (Pierard *et al.*, 1983). Often, these bacteria have been found to be resistant to many antimicrobials including the aminoglycosides and β-lactam antibiotics (Gill *et al.*, 1981). This situation has been found also with the collection of strains examined in this study. However, some strains that were highly resistant to imipenem (MICs > 128 mg/l) were susceptible to meropenem (MICs 2–8 mg/l). Other corynebacteria generally were highly susceptible to both carbapenems. Highly susceptible, also, were the *Listeria monocytogenes* strains examined. MICs of meropenem for the NCCLS quality control strains determined in agar dilution tests were the same on either Mueller–Hinton agar or Mueller–Hinton agar supplemented with 7% human blood. The range of MICs for *Staph. aureus* ATCC 29213 was 0·06–0·12 mg/l, that for *Esch. coli* ATCC 25922 0·016–0·03, and that for *P. aeruginosa* 0·25–1 mg/l.

Results with methicillin-resistant staphylococci

Meropenem and imipenem showed some activity against methicillin-resistant staphylococci, when tested in agar dilution with an inoculum of 10^4 cfu per spot (see Table I). In tests with a higher inoculum, i.e. in macrobroth dilution tests, MICs of these carbapenems were considerably higher (data not shown). This phenomenon resulted from the heterogeneous resistance to β-lactam antibiotics in such strains (Kayser *et al.*, 1972). Figure 1 shows the population analysis of four isogenic *Staph. aureus* strains on meropenem. Strain BB255 was the susceptible parent strain. Strain BB270 was obtained by introducing the methicillin resistance determinant *mec* from a wild type strain into BB255. Two main resistance levels were recognizable: a low basal level, displayed by all cells, and a second higher, but heterogeneous, level shown here by one in 10^3 cells. The phenotypically susceptible strain BB308, derived from strain BB270 by Tn*551*-insertion of Ω2003 into the chromosome, although harbouring the intact

Table I. Comparative activity of meropenem and other antimicrobials against Gram-positive bacteria

Organism group	Number	Drug	MIC (mg/l) geometric mean	range	50%	90%
Staph. aureus methicillin-susceptible	58	meropenem	0·14	0·06–0·25	0·12	0·25
		imipenem	0·04	0·016–0·06	0·03	0·06
		cefotaxime	2·45	1–8	2	4
		ceftazidime	12·75	8–32	16	16
		piperacillin	2·76	1–32	4	8
		ciprofloxacin	0.41	0·12–1	0·5	1
		gentamicin	0·42	0·06–>128	0·5	1
		vancomycin	0·99	0·5–2	1	1
		methicillin	2·23	1–4	2	4
		methicillin[a]	5·20	1–8	4	8
Staph. aureus methicillin-resistant	12	meropenem	1·33	0·25–8	2	2
		imipenem	0·59	0·06–32	0·5	1
		cefotaxime	25·40	2–>128	32	128
		ceftazidime	33·90	16–128	32	64
		piperacillin	57·02	8–>128	64	128
		ciprofloxacin	0·30	0·12–1	0·25	0·5
		gentamicin	25·40	0·12–>128	128	>128
		vancomycin	0·94	0·5–1	1	1
		methicillin	8·98	2–128	8	16
		methicillin[a]	35·92	16–>128	32	128
Coagulase-negative staphylococci, methicillin-susceptible	32	meropenem	0·13	0·06–1	0·12	0·12
		imipenem	0·02	0·016–0·06	0·03	0·03
		cefotaxime	0·81	0·5–4	1	1
		ceftazidime	5·66	4–16	4	8
		piperacillin	0·61	0·25–8	0·5	2
		ciprofloxacin	0·16	0·06–0·25	0·12	0·25
		gentamicin	0·16	0·016–128	0·12	0·25
		vancomycin	1	0·5–2	1	2
		methicillin	1·24	0·25–4	2	2
		methicillin[a]	1·22	0.06–4	2	4

Coagulase-negative staphylococci, methicillin-resistant	18	meropenem	3·30	0·25–32	2	32
		imipenem	1·21	0·016–64	0·5	64
		cefotaxime	16	4–>128	16	128
		ceftazidime	30·79	8–>128	64	>128
		piperacillin	15·40	1–>128	8	>128
		ciprofloxacin	0·28	0·12–32	1	8
		gentamicin	4	0·008–>128	16	128
		vancomycin	1·65	0·5–4	2	12
		methicillin	17·96	2–>128	16	>128
		methicillin[a]	87·09	4–>128	128	>128
Ent. faecalis	49	meropenem	5·03	2–16	4	8
		imipenem	1·07	0·5–2	1	2
		cefotaxime	174·85	0·5–>128	>128	>128
		ceftazidime	212·31	8–>128	>128	>128
		piperacillin	3·05	2–8	4	4
		ciprofloxacin	1·21	0·5–4	1	2
		gentamicin	6·54	0·5–32	8	16
Ent. faecium	13	meropenem	11·63	1–64	8	64
		imipenem	4·23	0·25–64	4	32
		cefotaxime	142·02	32–>128	128	>128
		ceftazidime	>128	>128	>128	>128
		piperacillin	17·75	4–>128	16	128
		ciprofloxacin	2·22	1–4	2	4
		gentamicin	16·91	4–64	16	32
Str. pyogenes	20	meropenem	0·01	0·008–0·016	0·008	0·008
		imipenem	0·01	0·004–0·008	0·008	0·008
		cefotaxime	0·01	0·008–0·03	0·016	0·016
		ceftazidime	0·20	0·12–0·25	0·12	0·25
		piperacillin	0·07	0·03–0·12	0·06	0·12
		ciprofloxacin	0·59	0·25–1	0·5	1
		gentamicin	13·45	4–16	16	16

continued overleaf

Table I. *contd*

Organism group	Number	Drug	MIC (mg/l) geometric mean	range	50%	90%
Str. agalactiae	10	meropenem	0·04	0·03–0·06	0·03	0·06
		imipenem	0·02	0·016–0·03	0·016	0·03
		cefotaxime	0·05	0·03–0·06	0·06	0·06
		ceftazidime	0·5	0·5	0·5	0·5
		piperacillin	0·25	0·25	0·25	0·25
		ciprofloxacin	0·93	0·5–2	1	1
		gentamicin	59·71	32–64	64	64
Streptocooccl groups C and G	19	meropenem	0·01	0·008–0·12	0·016	0·016
		imipenem	0·01	0·004–0·016	0·008	0·008
		cefotaxime	0·02	0·016–0·06	0·03	0·03
		ceftazidime	0·24	0·12–1	0·25	0·25
		piperacillin	0·10	0·06–0·12	0·12	0·12
		ciprofloxacin	0·80	0·5–1	1	1
		gentamicin	16·56	8–32	16	16
Str. pneumoniae	20	meropenem	0·03	0·008–0·25	0·016	0·03
		imipenem	0·01	0·008–0·12	0·008	0·03
		cefotaxime	0·03	0·016–1	0·03	1
		ceftazidime	0·39	0·12–8	0·25	4
		piperacillin	0·06	0·03–1	0·03	0·5
		ciprofloxacin	1·57	1–4	1	2
		gentamicin	15·45	8–32	16	32
Str. bovis	14	meropenem	0·04	0·016–4	0·03	0·25
		imipenem	0·02	0·008–0·5	0·016	0·25
		cefotaxime	0·18	0·03–16	0·12	1
		ceftazidime	2	0·5–128	1	8
		piperacillin	0·43	0·06–8	0·5	8
		ciprofloxacin	2	1–4	2	2
		gentamicin	5·13	2–8	4	8

Streptococcus	28	meropenem	0·04	0·016–4	0·03	0·25
sanguis		imipenem	0·02	0·008–0·5	0·016	0·25
milleri		cefotaxime	0·18	0·03–16	0·12	1
mitior		ceftazidime	2	0·5–128	1	8
salivarius		piperacillin	0·43	0·06–8	0·5	8
mutans		ciprofloxacin	2	1–4	2	2
		gentamicin	5·13	2–8	4	8
C. jeikeium	17	meropenem	0·85	0·001–>128	1	8
		imipenem	2·45	0·001–>128	1	>128
		cefotaxime	20·43	0·016–>128	16	>128
		ceftazidime	108·74	0·5–>128	>128	>128
		piperacillin	33·33	0·06–>128	64	>128
		ciprofloxacin	0·59	0·06–16	1	2
		gentamicin	144·65	0·016–>128	>128	>128
Other corynebacteria	18	meropenem	0·04	0·001–8	0·03	0·12
		imipenem	0·02	0·004–2	0·016	0·06
		cefotaxime	0·40	0·016–>128	0·5	2
		ceftazidime	5·66	0·25–64	8	32
		piperacillin	1·71	0·36–>128	2	4
		ciprofloxacin	0·15	0·06–1	0·125	0·5
		gentamicin	0·382	0·03–16	0·25	4
Rhodococcus equi	6	meropenem	0·14	0·016–0·5		
		imipenem	0·08	0·008–0·5		
		cefotaxime	0·89	0·06–4		
		ceftazidime	14·2	0·5–64		
		piperacillin	4·49	0·06–16		
		ciprofloxacin	0·79	0·25–2		
		gentamicin	0·89	0·06–16		
Erysipelothrix rhusiopathiae	4	meropenem	0·04	0·03–0·06		
		imipenem	0·016	0·008–0·03		
		cefotaxime	0·21	0·12–0·5		

continued overleaf

Table I. *contd*

Organism group	Number	Drug	MIC (mg/l) geometric mean	range	50%	90%
		ceftazidime	1	0·5–2		
		piperacillin	0·12	0·06–0·25		
		ciprofloxacin	0·09	0·06–0·25		
		gentamicin	181·02	128–>128		
L. monocytogenes	11	meropenem	0·10	0·06–0·12	0·12	0·12
		imipenem	0·10	0·06–0·12	0·12	0·12
		cefotaxime	43·71	8–128	64	64
		ceftazidime	240·52	128–>128	>128	>128
		piperacillin	1·77	0·5–4	2	2
		ciprofloxacin	1	1	1	1
		gentamicin	0·37	0·25–1	0·25	0·25
Bacillus spp.	24	meropenem	0·17	0·03–2	0·12	1
		imipenem	0·10	0·016–4	0·06	2
		cefotaxime	1·54	0·008–64	2	64
		ceftazidime	13·45	0·25–>128	8	128
		piperacillin	0·30	0·016–2	0·25	1
		ciprofloxacin	0·13	0·016–1	0·12	0·5
		gentamicin	0·47	0·06–4	0·5	2

*MICs were determined on Mueller–Hinton agar supplemented with 4% NaCl.

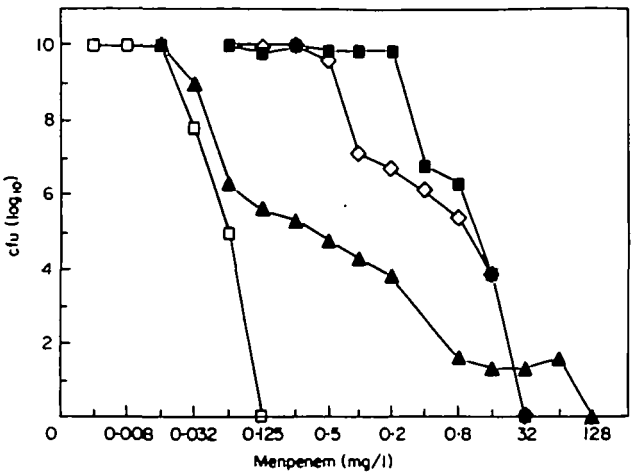

Figure 1. Population analysis of four isogenic *Staph. aureus* strains on meropenem. □, Methicillin-susceptible strain BB255; ■, methicillin-resistant strain BB270; ▲, methicillin-susceptible strain BB308 derived from BB270 by Tn*551* insertion; ◇, methicillin-resistant revertant strain r2 derived from BB308, with a deletion within the chromosome.

methicillin resistance determinant *mec*, had lost the expression of low level resistance and the high level resistance was impaired. Strain r2 was a revertant from BB308 with a deletion within the chromosome. This strain had regained both resistance levels and showed a resistance pattern similar to BB270. (For a more detailed description of the strains see Berger–Bächi *et al.*, 1986.) The patterns shown in Figure 1 are very similar to results of population studies with imipenem (Berger–Bächi *et al.*, 1986). Heteroresistance to meropenem was also observed in strains of coagulase-negative staphylococci harbouring the *mec*-determinant (data not shown). The results obtained by measuring the affinity of meropenem and imipenem to the PBPs of *Staph. aureus* were in accordance with the population studies (Figure 2). Whereas PBPs of the susceptible strain BB255 were saturated by low amounts of the antibiotics (Figure 2(a)), high amounts were necessary to saturate PBP 2′, the biochemical correlate of methicillin-resistance, in strain BB270 (see Figure 2(b)).

Bactericidal activity of meropenem

Examination of the bactericidal activity of meropenem and comparative agents initially was carried out by conventional MBC tests performed in triplicate. Although great care was taken in performing these tests, results were often inconsistent, especially with staphylococci, owing to methodological problems (see Taylor *et al.*, 1983). We therefore decided to study the bactericidal potential of the drug in a kinetic system. Figure 3 shows the killing curves obtained with meropenem at various multiples of the MIC against three representative strains (one each of *Staph. aureus, Streptococcus agalactiae* and *Enterococcus faecalis*). The drug killed efficiently, even at rather low concentrations. The rate and the degree of killing of the *Staph. aureus* was less pronounced at four and eight times than at one and two times the MIC (Figure 3(a)). This well-known paradoxical effect was also observed with imipenem and flucloxacillin (data not shown). Not all the staphylococcal strains examined, however, exhibited this beha-

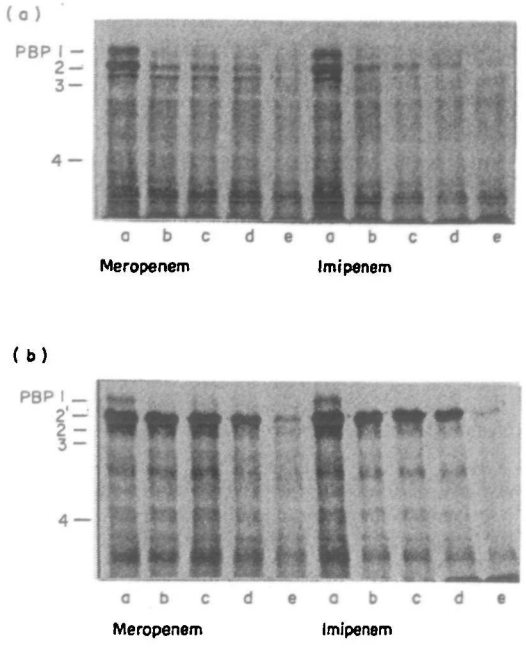

Figure 2. Fluorograph of penicillin binding proteins of (a) methicillin-susceptible *Staph. aureus* BB255 and (b) methicillin-resistant strain BB270. Membrane preparations were prepared as described and preincubated with various concentrations of either meropenem or imipenem, before treatment with ^{3}H-labelled penicillin. Lanes: a, 0; b, 0·5; c, 5; d, 50; and e, 500 mg/l of either meropenem or imipenem, respectively.

viour. Figure 4 shows the killing curves of meropenem in comparison with imipenem and further bactericidal antimicrobials at four times the MIC of each antibiotic for *Ent. faecium*, *C. jeikeium*, and *L. monocytogenes*. The bactericidal activities of the β-lactam antibiotics tested were approximately equal. The rate of killing of meropenem and comparative drugs for all species was low during 6 h of incubation, but increased by incubating for 24 h.

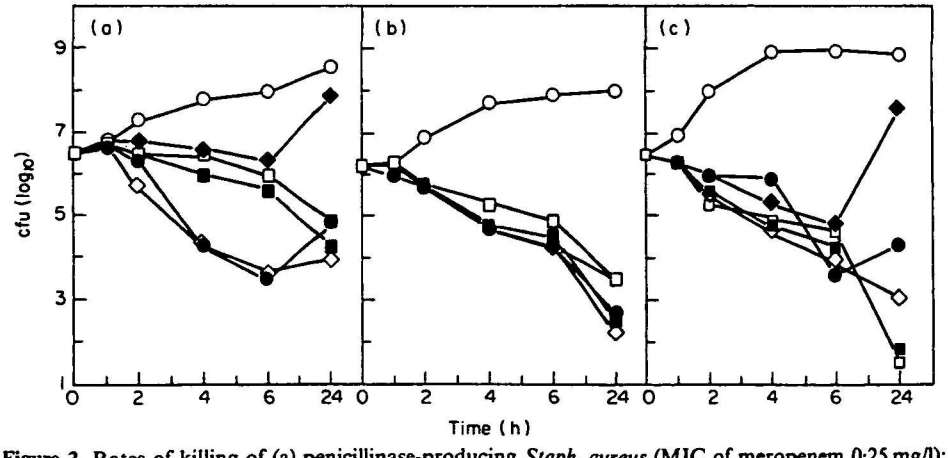

Figure 3. Rates of killing of (a) penicillinase-producing *Staph. aureus* (MIC of meropenem 0·25 mg/l); (b) *Ent. faecalis* (MIC 4 mg/l); (c) *Str. agalactiae* (MIC 0·016 mg/l), by various concentration of meropenem. ○, Control; ◆, ½ × MIC; ●, 1 × MIC, ◇, 2 × MIC; ■, 4 × MIC; □, 8 × MIC.

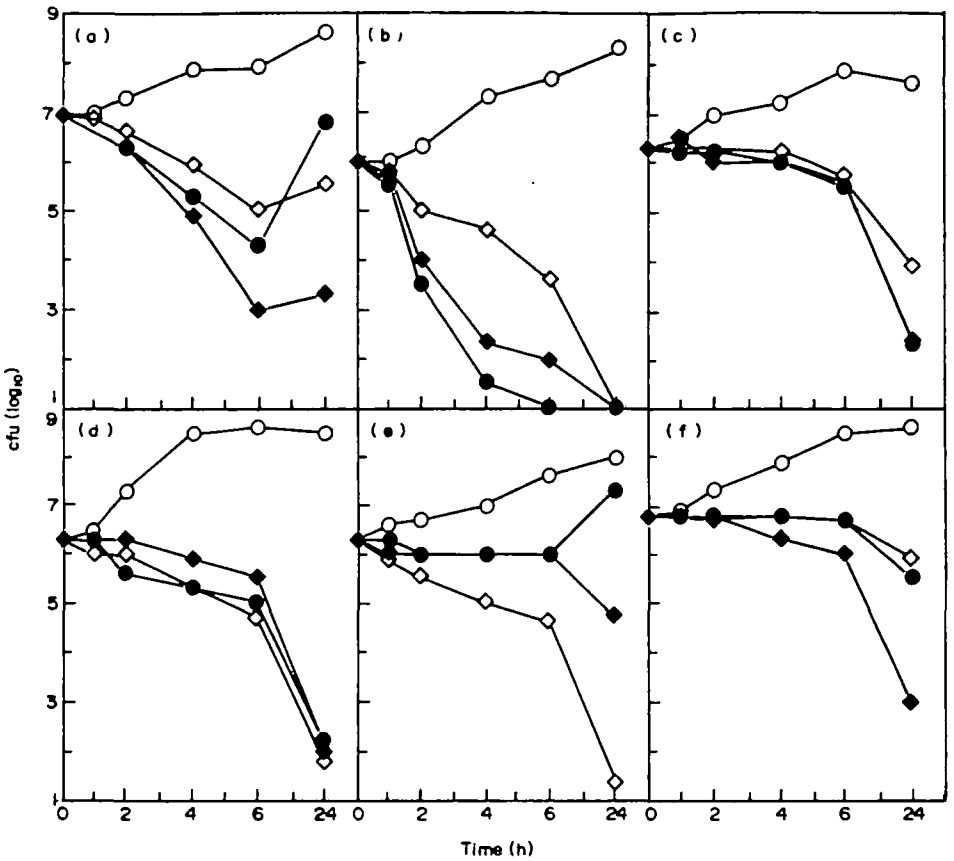

Figure 4. Comparison of the rate of killing of Gram-positive organisms by 4 times the MIC of ◆, meropenem; ●, imipenem; ◇, various bactericidal antimicrobials. ○, Growth control. (a) Penicillinase-negative *Staph. aureus* (MIC of meropenem 0·06; imipenem 0·008; flucloxacillin (◇) 0·25 mg/l). (b) *Staph. epidermidis* (MIC of meropenem 0·12; imipenem 0·03; vancomycin (◇) 2 mg/l). (c) *Ent. faecium* (MIC of meropenem 4; imipenem 1; vancomycin (◇) 4 mg/l). (d) *Strep. pyogenes* (MIC of meropenem 0·016; imipenem 0·004; benzylpenicillin (◇) 0·016 mg/l. (e) *C. jeikeium* (MIC of meropenem 2; imipenem 8; vancomycin (◇) 1 mg/l). (f) *L. monocytogenes* (MIC of meropenem 0·06; imipenem 0·06; ampicillin (◇) 0·25 mg/l).

Discussion

Meropenem was shown to be an excellent antibiotic against most species of Gram-positive bacteria. In particular, the drug exhibited some activity against methicillin-resistant staphylococci, when tested in agar dilution with an inoculum of 10^4 cfu per spot. However, the typical characteristics of methicillin-resistant staphylococci, namely heteroresistance (Figure 1), and the influence of incubation temperature, duration of incubation, and sodium chloride content of the agar medium on the phenotypic expression of resistance (data not shown), were also observed with meropenem (data not shown). Thus, as with all other β-lactam antibiotics (Kayser, 1980), meropenem does not seem likely to be a useful agent in the treatment of diseases caused by methicillin-resistant staphylococci. Meropenem exhibited high activity against all streptococcal species examined. Against *Enterococcus faecalis*, meropenem was approximately four times less active than imipenem, but showed similar activity to piperacillin,

whereas, as expected, the cephalosporins were not active at all. Meropenem was as bactericidal as other β-lactam agents against most of the examined organisms in kinetic studies. Only poor bactericidal activity of the β-lactams was observed against *Ent. faecium, C. jeikeium* and *L. monocytogenes.*

In summary, this new experimental carbapenem antibiotic exhibited nearly identical properties to imipenem against Gram-positive organisms. Its greater stability to the dehydropeptidase-1 enzyme of the human kidney and its superior activity against Gram-negative organisms, including *Pseudomonas* spp., justify clinical trials.

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